Application No.: 09/920,033

## REMARKS

Claims 20, 23, and 26 are amended herein. Claim 20 is amended to be consistent with claim 1. Claims 23 and 26 are amended so that they properly depend from amended claim 20. Support for the amendments to the claims can be found throughout the specification, e.g., at least at page 90 and 91. The amendments do not include new matter.

**The Outstanding Rejections**

35 U.S.C. § 112, First Paragraph

Claim 20 stands rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicant respectfully traverses the rejection. However, in order to expedite prosecution, Applicant has amended claim 20 to specify that the claimed compounds specifically hybridize to nucleotides 1-114 or nucleotides 151-14121 of SEQ ID NO:3. These nucleotide ranges are identical to those of the other independent claims, which do not stand rejected under 35 U.S.C. § 112, first paragraph. Applicant respectfully requests reconsideration of the rejection of claim 20.

Applicant reserves the right to pursue the subject matter previously presented in claim 20 in subsequent related applications.

35 U.S.C. § 102(b)

Claim 20 further stands rejected as anticipated by Tang *et al.* The Examiner contends that the antisense oligonucleotide of Tang *et al.* would specifically hybridize to nucleotides 149-154 of SEQ ID NO:3. Applicant respectfully disagrees. The 20-mer of Tang et al. would hybridize with nucleotides 129-**148** of SEQ ID NO:3, not 129-154 as described by the Examiner. Thus, the antisense oligonucleotide would not specifically hybridize to nucleotides 149-154 of SEQ ID NO:3. Moreover, amendment to claim 20 herein renders the rejection moot.

35 U.S.C. § 103(a)

Claims 1-14, 20-23, and 27 stand rejected as assertedly being unpatentable over Chan *et al.*, (WO/01/12789) in view of Branch, Monia et al., and Agrawal *et al.* Chan *et al.* is cited for purportedly disclosing a ribozyme targeting position 6679 of SEQ ID NO:3. Branch is cited for disclosing that antisense oligonucleotides should be 17 base pairs or longer. Monia

*et al.* is cited for disclosing chimeric and modified antisense oligonucleotides and use of such oligonucleotides in pharmaceutical compositions. Agrawal is cited as purportedly providing motivation for designing oligonucleotides targeting various regions of target mRNA. From these disclosures the Examiner asserts it would have obvious to modify the disclosure of Chan *et al.* to provide the presently claimed non-catalytic compounds and compositions comprising said compounds.

Although Chan et al. is recognized as (1) not disclosing compounds of claim 1 and (2) not disclosing the non-catalytic compounds comprising the various modifications in the present claims, or compositions thereof, the Examiner asserts that one of ordinary skill in the art would be motivated to modify Chan et al. (1) to design antisense oligonucleotides of about 17 nucleobases in length as provided by Branch in order to maximaize target specificity, (2) to include modified linkages, modified sugar residues and modified nucleobases as provided by Monia *et al.* to maintain nuclease resistance and cellular uptake, and (3) to design antisense oligonuclotides to ApoB to study the function of the gene. Moreover, the Examiner contends that it would have been obvious to substitute the ribozymes of Chan *et al.* with the non-catalytic compounds of the present claims, because both are nucleic acid based inhibitors and both function to reduce the expression of a target mRNA, i.e. are functionally equivalent.

Applicant respectfully disagrees with the rejection. The claimed subject matter as a whole is not suggested by the combined disclosures relied on by the Examiner and nothing in these disclosures suggests that the primary reference can or should be modified to provide the invention as claimed.

Everything in Chan *et al.* is directed to ribozymes, which are a distinct class of molecules compared to the claimed compounds. Page 1, line 3, states "[t]he present invention is directed to an enzymatically active RNA, *i.e.*, a ribozyme, that specifically cleaves the mRNAof apolipoprotein B (ApoB)."). The Examiner asserts that, because both ribozymes and antisense compounds are nucleic acid based inhibitors and both function to reduce expression of a target mRNA, the two can be substituted, *i.e.*, are interchangeable. (Office Action, page 8). This assertion is unsupported and does not take into consideration the structural and functional differences of ribozymes and non-catalytic antisense compounds. Unlike the compounds presently claimed, ribozymes include a region that hybridize to a target and include a catalytic site *that does not hybridize to the target*. The catalytic site includes a degree of secondary structure that is not found in non-catalytic

antisense compounds, and because of this secondary structure, the catalytic site is not complementary to and cannot hybridize to the target nucleic acid. Ribozymes are therefore *only in part* complementary to a target. An non-catalytic antisense molecule, on the other hand, has no such catalytic region and tend to hybridize to the target over its entire length, depending on the degree of complementarity. Thus, ribozymes and non-catalytic antisense compounds are chemically and structurally distinguishable.

Moreover, ribozymes function to inhibit target nucleic acid expression in a way completely different from non-catalytic antisense molecules. Ribozymes specifically cleave a target RNA while *non-catalytic* antisense compounds do not. Thus, the mechanism by which these two types of compounds inhibit expression of a target are not the same. Given the chemical, structural, and functional differences of ribozymes and non-catalytic antisense compounds, Applicant respectfully disagrees with the Examiner's unsupported assertion regarding the recognition by one of skill in the art of the interchangeability of the two types of molecules.

The secondary references are directed to general optimization guidelines for uses of antisense molecules. The secondary references do not disclose or suggest a recognition in the art of the interchangeability of ribozymes and non-catalytic antisense molecules. There is no suggestion in the cited art to excise the catalytic portion of the ribozyme of Chan *et al.* to produce a non-catalytic compound of the present claims. Moreover, the cited art does not provide a reasonable expectation for success in inhibiting expression of a target nucleic acid by (1) removing the catalytic portion of a ribozyme or (2) targeting a non-catalytic compound to the target site of a ribozyme. Thus, the rejection fails to provide motivation for the modification of the ribozyme teachings of Chan *et al.* to arrive at the non-catalytic compounds of the present invention, and even if such motivation existed, the rejection fails to establish that one of skill in the art would have a reasonable expectation of inhibiting ApoB expression using the modified ribozyme of Chan et al. Applicant respectfully requests withdrawal of the rejection of claims 1-14, 20-23 and 27 under 35 U.S.C. § 103(a).

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**Conclusion**

Applicant respectfully requests issuance of a timely Notice of Allowance. The Examiner is invited to contact the undersigned with any comments or suggestions that might expedite the issuance of the application.

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Respectfully submitted,

By _____

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